Prognostic Factors in Prostate Cancer:  
A Review Article

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Abstract

Background:  
Prostate cancer is widely known to vary substantially in aggressiveness. There is also significant potential morbidity associated with aggressive curative treatment. So, there is a tremendous interest in the development of prognostic factors that could guide management decisions that allow treatment to be tailored and individualized.

This review seeks to identify the traditional tumour related prognostic factors, emerging biomarkers of prognostic importance as well as patient and environment related prognostic factors in prostate cancer.

Method:  
The PubMed database was searched for all existing literature. Also, references were made to some bibliographies cited in the available literature.

Conclusion:  
Majority of prostate cancer may not progress to clinically significant disease. Prognostic factors have therefore become important to predict tumour progression and eventual outcome.

Keywords: prostate cancer, prognostic factors, tumour makers, biological markers.

Introduction  
Prognosis refers to forecast of possible course and outcome of a disease. Bailey1 defined prognosis as a reasoned forecast concerning the course, pattern, progression, duration and end of a disease. For a patient, it reflects the chances of survival.

Prognostic factors are variables that account for some of the heterogeneity associated with the expected course and outcome of a disease1. These factors are important in understanding of the natural history and course of a disease as well as in predicting treatment outcome.

The incidence of Prostate cancer is increasing in this environment. With ageing population, improvement in economic situation and changing social lifestyles, it is expected that prostate cancer will be very common male malignancy in nearest future. Similarly, the socio demographics factors in prostate cancer are changing, with younger males affected and aggressive disease seen in this environment compared with the pattern in developed world.

The implication of the variables is that treatment must be individualized for each patient; no single type of protocol will satisfy the various tumour biology and variables. Similarly, for better treatment outcome and survival, the concept of multidisciplinary and multi modality approach to prostate cancer cannot be overemphasized.

Based on the clinical findings and on the variables available, the treatment should be tailored to meet the patient's needs holistically. In other words, the treatment should ideally be individualized. For example, which class of patients will benefit from watchful waiting, conservative management, radical surgery, surgical castration, is identified and
complications avoided. Similarly, it will form a basis for which chemotherapy regimen are used on evidence-based medicine. It will reduce the common problems of inadequate treatment, over treatment, inadequate dosages, and delay in referral for radiotherapy and chemotherapy.

Prognostic factors become even more important in prostate cancer where a large number of cases are unlikely to become clinically manifest and aggressive treatment carry significant potential morbidity. Stanford and colleagues in a study of complications after surgical therapy for localized disease in an unselected population-based cohort reported that at more than 18 months after radical prostatectomy, 8.4% of men were incontinent and 41.9% reported their sexual performance as a moderate to large problem. It is therefore important to apply prognostic factors in making prostate cancer treatment decisions.

Several independent prognostic factors have been proposed for prostate cancer. See Table 1. These may be classified into:

1. Tumour related prognostic factors.
2. Patient related prognostic factors.
3. Environment (including financial) related prognostic factors.

### Tumour related prognostic factors

#### 1. Histological features

##### a. Tumour type

The uncommon histologic variants of prostate cancer can be associated, with rapid progression. The presence of small cell carcinoma and poorly differentiated tumours expressing neuroendocrine makers are harbinger of poor prognosis.

Mucinous carcinomas, rarely respond to hormonal therapy and often cause bone metastasis. Adenoidcystic carcinoma is also associated with distant metastasis at diagnosis. Small cell and neuroendocrine cancer are associated with a uniformly poor prognosis.

##### b. Tumour grade

The microscopic grade of a prostate cancer correlates significantly with the local extent of the disease, response to various therapies and overall disease outcome.

The histological Gleason score of the adenocarcinoma of the prostate is a good and an established prognostic factor. Univariate and multivariate analyses of prognosis in prostate cancer almost always identify Gleason grade as one of the most significant predictors of patient outcomes. Two important studies have demonstrated a good correlation between the prognosis of prostate cancer and Gleason score.

##### c. Tumour stage

The pathological stage of prostate cancer is one the most important independent prognostic factor. Most often, treatment is determined by stage of disease. The presence of perineural invasion in the needle biopsy specimen has been reported to be specific marker for capsular penetration of the tumour in prostatectomy specimen. Seminal vesicle invasion is associated with high grade, lymphatic metastasis and poor prognosis. Also, positive margin of resection significantly affect disease outcome and correlate with high pre-operative PSA, high grade and poor prognosis. The presence of nodal metastasis is associated with significant tumour progression and poor prognosis. Bone, liver and other visceral metastases, often herald progression to an ultimate fatal outcome.

#### 2. Tumour-specific protein /molecular markers

##### A. PSA

The values of total PSA (tPSA), free (fPSA) and PSA complexed to α1-antichymotrypsin (PSA-ACT) are all independent prognostic factors of prostate cancer. Serum PSA level is a strong prognostic determinant of outcome following radiotherapy for prostate cancer and appears to add prognostic information independent of tumour stage and grade.

Also, after radical prostatectomy a rising serum PSA level almost always precedes clinical recurrence of the cancer. The clinical significance of pre-treatment serum PSA value studied by Kariyama and colleagues revealed that serum PSA can be used to predict the stage and prognosis of prostate cancer.

In particular, pre-operative serum PSA levels are highly predictive of tumour burden and risk of recurrence after radical prostatectomy.

##### b. DNA ploidy

Many retrospective studies have shown that aneuploid DNA content in prostate cancer
independently predicts a poor prognosis\(^{23, 24}\). Aneuploidy has generally been associated with poor differentiation and more aggressive tumour in comparison with diploid lesion and this holds for prostate cancer. About 85% of patients with organ confined prostate cancer treated with radical prostatectomy have diploid tumours.

c. **Microvessel density (MVD)**

Tumour growth beyond a certain size requires angiogenesis. Tumour angiogenesis correlates with poor outcome in prostate cancer\(^{25}\). Significantly higher microvessel counts have been obtained in areas of adenocarcinoma than in benign tissues of radical prostatectomy specimen. Bore and colleagues\(^{26}\) demonstrated that MVD was a significant predictor of shorter disease-specific survival in the entire cancer population.

3. **Tumour suppressor genes**

a. **P53**

Increase expression of P53 is associated with point mutations of one allele of P53 gene and loss in others. Thomas and colleagues\(^{27}\) as well as Shurbaji and colleagues\(^{28}\) following immunohistochemical evaluation of P53 gene, chronicled that mutations of P53 genes are involved in the carcinogenesis of prostate cancer. They also noted that it is associated with an aggressive subset of prostate cancer.

b. **PTEN/AKTI-1**

The PTEN (Phosphatase and Tensin homolog detected from chromosome 10), a tumour suppressor gene is deleted or mutated in a wide variety of malignant neoplasms and also in prostate cancer\(^{29, 30}\). Loss of expression of PTEN has been associated with down-regulation of cyclin-dependent kinase inhibitor, P27 and poor prognosis with increasing tumour grade and stage of prostate cancer\(^{31}\).

4. **Oncogene**

a. **Her-2/neu (Cerb-b2) gene**

The presence of Her-2/neu gene amplification or over expression is associated with poor outcome\(^{32, 33}\). Assessing for Her-2/neu is a routine practice in breast cancer but not so in prostate cancer. This is because unlike in breast cancer, randomized clinical trial (RCT) using Her-2/neu monoclonal antibody- trastuzumab (Herceptine) has not shown significant response in prostate cancer\(^{34}\).

5. **Androgen receptor (AR)**

Androgen receptor loss or mutation and lack of benefit from hormonal treatment have been associated with high grade disease and poor outcome. AR expression can be heterogeneous in prostate cancer, which reflects AR gene instability\(^{35}\). Mutation in the coding region of the AR gene has been found both in the untreated prostate cancer and hormone refractory prostate cancer (HRCP). Segawa and colleagues\(^{36}\) demonstrated that AR expression was significantly lower in adenocarcinoma than in non-tumour prostate tissues. They found that there is significant correlation between progression free survival and AR expression.

Similarly, the results of Miyoshi and colleagues\(^{37}\) showed that AR expression level in HRCP specimen was significantly lower than that in previously untreated prostate cancer or benign prostatic hyperplasia (BPH) specimens. The greater AR heterogeneity pattern seen in HRCP may be due to greater genetic instability in such tumours. In other words the growth factors may exhibit their effect via crosstalk with AR\(^{38}\). Therefore AR heterogeneity may be used as an independent predictor of response and sign of disease progression\(^{39}\).

6. **Cell proliferation markers**

a. **Ki-67**

Ki-67 is one of the several cell-cycling-regulating proteins. It is a DNA-binding protein, which is expressed in all phases of cell cycle but undetectable in resting cells\(^{40}\). Ki-67 index is higher for carcinomas than for hyperplastic glands. Within carcinomas, ki-67 indices in patients with metastatic disease were significantly higher than in those without metastasis.

b. **S-phase fraction.**

S-phase fraction (SPF) is the proportion of cells in the S-phase of the cell-cycle. High SPF is associated with rapid tumour proliferation, shorter overall survival and shorter time to local progression and metastasis in clinically localized prostate cancer\(^{41}\).

7. **Cell adhesion molecules**

a. **E-cadherin**

E-cadherin is an important adhesion molecule in epithelial cells. Reduction or loss of E-cadherin level has been found in malignant prostate speci mens\(^{42}\). Patients showing low immunohistochemical expression of E-cadherin
have on average shorter survival than patients with higher immunohistochemical expression.

**Patient related factors**

1. **Age**
The role of age of the patient as a significant prognostic factor in prostate cancer engenders debates. Harold and colleagues in analysis of 567 patients undergoing external beam radiotherapy (EBRT) found that age more than 65yr was a significant predictor of distant metastasis and poor outcome at 15yr. Obek and colleagues suggested that young age might be an independent favorable prognostic factor for disease recurrence after radical prostatectomy. Freedland and colleagues also found that young men had more favorable outcomes after radical prostatectomy than older men, which made younger patients suitable subjects in screening.

2. **Race**
The highest prostate cancer incidence and mortality have been reported in blacks. Race is a well known risk factor for developing prostate cancer. However this disease also behaves differently in men of different races. Whether this is due to patient related factors or to external factors is not clear yet.

Dasal and colleagues suggest that racial difference between Blacks and Caucasians in survival prognosis for prostate cancer was to a large extent the result of socio-economic status.

3. **Co-morbidities and Karnofsky Performance Status**
Diabetes mellitus, obesity, cardiac failure, hypertension, bleeding disorders, Karnofsky Performance Status are established poor independent outcome parameters in cancer patients.

Karnofsky Performance Status (KPS):
- **100%** Normal; No complaints
- **90%** Normal activities; minimal signs or symptoms
- **80%** Normal activities with effort. Some symptoms
- **70%** Caring for self; unable to work
- **60%** Needs occasional assistance but able to care for most needs
- **50%** Needs considerable assistance and frequent medical care
- **40%** Disabled; needs special care
- **30%** Severely disabled; needs hospital care
- **20%** Very ill. In hospital; needs supportive care
- **10%** Moribund.
- **0%** Dead.

As depicted above, the lower the KPS, the worse the patient's outcome, not only in prostate cancer, but in all malignancies.

**Environmental factors**

1. **Socio-economic status**
Studies have found reduced access to healthcare due to poor socio-economic status and this contributes to higher mortality rate from prostate cancer. It has been shown that among patients of high socio-economic class, even the elderly with low-risk prostate cancer receives some form of treatment. Financial constraint has been found to contribute to late presentation, poor treatment compliance, loss to follow up and poor treatment outcome in cancer patients in our environment.

2. **Access to quality health care.**
This is influenced by myriads of factors including the socio-economic factors, cultural practices, demography and national health-care policies. The impact is not only on outcome of prostate cancer but many disease entities. The National Health care policy which is absent in most developing countries influence the availability of facilities and expertise.

| Reference | NCCN Clinical Practice Guidelines in Oncology: Prostate cancer 2005 |

**Table 1: Table showing important prognostic factors in Prostate Cancer**

<table>
<thead>
<tr>
<th>TUMOUR RELATED</th>
<th>HOST RELATED</th>
<th>ENVIRONMENT RELATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSENTIALS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNM Categories</td>
<td>PSA</td>
<td>Gleason Score</td>
</tr>
<tr>
<td>ADDITIONAL</td>
<td>PSA Velocity</td>
<td>PSA Doubling Time</td>
</tr>
<tr>
<td>% Positive Biopsy</td>
<td>DNA Ploidy</td>
<td>Margin Status</td>
</tr>
<tr>
<td>NEW AND PROMISING</td>
<td>Ki 67</td>
<td>MIBI Microvessel Density</td>
</tr>
</tbody>
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**Conclusion**
A large number of prostate cancers may never progress to clinically significant disease. Tumour related preoperative and postoperative prognostic
factors are important to predict prostate cancer outcome. The classical tumour related prognostic factors in prostate cancer are TNM stage, the serum PSA level and Gleason score. Other valuable tumour related prognostic factors like biomarkers (DNA ploidy, MVD, PTEN/AKT/1, AR, Ki-67, E-cadherin, S-phase fraction) remains to be applied routinely in clinical practice despite extensive literature that support their usefulness. Apart from tumour related factors, prognosis is also determined by the patient's personal data related to age, race, co-morbidities and even his individual life expectancy.

The health provider and national health policies as well as access to quality health-care are also important prognostic factors, even more so in our sub-region.

The efforts to provide optimal health-care for everybody everywhere may be seen as utopia, but somehow it does not seem right that someone's socio-economic or demographic situation affect his prognosis significantly. Yet, this happens often in our country and there is need for change.

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